

21st. Sept.

* Ragnar - review on leukemia

T. Müller.

* publication - in prem. re hemoygenase.

Results not shown re hemoygenase i.d.

where does the debiting component for antioxidants come in?

Stress response - put back in function....? Phosphatase inhibition?

∴ what is the "effect" of stress on the epigenetic level.

Glutathione depletion may be different in diff cell types.

e.g. bronchial - & depletion
but lung tissue no effect found (review from Müller).

Future plans investigate different candidates - sulphhydryl ^{reactive compounds}
heavy metal ions [Cd⁺⁺]
NO? + relatives (peroxynitrate)

Concentration of Cd⁺⁺ in PBS?

to find out in order to judge relevance

Cd⁺⁺ = sulphhydryl reactive;

No diff in media w pure gas vapour phase....

What is the ultimate objective -

Main aim at present is to understand the mechanism & to learn about the compounds which are doing this.

2 aspects - may be separately controlled - ① phosphatase inhibition
(but may lead to effects on apoptosis)

② Inhibition? of cellular defense reactions.....

protein phosphatases I & IIa = primary phosphatases involved in

tumor promoting - control of cdc p34 etc etc.....

* Book Tobacco smoking & Nutrition: in Proceedings from conference Univ. Kentucky

* Fleckenstein review: New Scientist 19 June 1993.

2028541459

Schlage:-

PTE = Rat tracheal epithelium
RNE = Rat Nasal epithelium.

Mouse C 10T $\frac{1}{2}$. CFE... range finding preliminary.
2-stage transformation assay.

definition of cell lines - related to early response changes.
FAST system - distortion from blocking procedure: thermal blocking.
scanner & evaluation software:--
Cytokeratin expression. Normalized on 97,000 hist protein.
∴ determine hist with accuracy on calibration curve.

Transformation

2 stage (1 stage rejected, not good for routine!)
7 arrays in 2 years - w smoke condensates - yes/no only,
but not able to distinguish between condensates.
To enhance sensitivity? - match initiator conc.; frequency of provider
= 43 day cycle. provider after 6 days -
varied (4) initiator conc 12 weekly provider removal.
but TPA found to act independent of initiator!

Why wait initiator in response greater w lower dose of TPA?
Improved for TPA - but not for N smoke. cytotoxicity?
Are we sure that there is an initiation, promotion situation

Find complementary end point, for screening

Metabolic cooperation - dye lucifer yellow

NS sensitive to passage NP & confluence.

TPA reduces cell-cell communication as detected by fluorescence
dye transfer. at dose 500x lower than in transformation assay.
CSC - in range of 1 & 2 stage transformation final effect late
at minimum dose

some hints of low communication index in 70x derived transformed
cells.

histo activity with Biotin staining-

Mitochondria staining Tundownline - diff between transformed
and untransformed in ultrastructural activity.

Oey.

Cytotox - Kenacid Blue

N. Red Assay - uptake - by viable cells. - growth inhibition
- released by dead prelabelled cells. death.

Results:- +ve control SDS. - same concs diff EC50 values.

Uptake assay - 24h incubation

Release assay = 1h (w SDS) or 1min -

diff in EC50s - enormous!

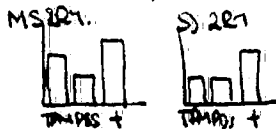
Re release - lost at combination of different nations and comparison
of different cigarettes.

N.B. PBS = QVP.

Neutral red release w ZR: TPM > QVP. QVP + TPM > QVP/TPM.

MS. (combination of TPM & PBS not as much as sum of 2 columns!)
(but w 124F - TPM & PBS + recombination does work!).

SS: TPM > QVP Recan.



Miscellaneous:- analysis of cell size - counter counter w image analysis
3 cell lines VPA, Balb 3T3 & Swiss 3T3.

Could be used for QA of cell lines and as a possible endpoint
for cytotoxicity.

Investigation of including X-ray as positive control.

URSUS S9/3S

TPM = no EC50 values - never gets down to 50% value!

QVP (PBS) - 124F > 3S > S9

NRO = Kenacid blue.

Recan. > than PBS alone!

WIDE

Nicotine toxicity:- cytotox at v. high concs (mMol/L)

Diff curves w NRO comp to Kenacid Blue.

so what happening w nicotine as well.

photographs - vacuolation - lysosomes which stain w neutral
red: initially = higher than control = dose dependent but
reversible - in after nicotine addition - ~~steady~~



2028541462

N.B. also H. pylori toxin & vaccination
Mechanism of cytoplasmic vaccination

↳ vaccination seemingly hypodermal? - do take up neutral red
which indicates be lysosomes, not ER.
N.B. collagen - does not induce vaccination (because it is not an antigen)

Release v uptake - uptake means a more complex procedure than
the release.

Method -



Cytometry: - in vitro: - microscopic MN
Polymers

In vivo - lung clearance after BSS

Method dup centrifugal elutriation.

Paravaginal blood seque.

Colony Differs all counting of red blood & free lung cells.

MN-v79, by CG smoke - induce? - clastogenic or aneugenic?

N.B. lower blood - ∴ manual staining tech. - checks reproducibility

Now should develop flow cytometry method

In vivo lung clearance after inhalation of BSS. 124F
subcutaneous inhalation study in rats - contact future inhalers
studied in BSS. - Pilot study - experience is methods for
measuring lung clearance; lung for burden & cell damage.
fluorescent latex beads - average day 0, 1, 3 & 11.

beads counted with flow cytometry

Clearance of lung - No diff! - but there is a
reduction of particle burden to around 70% in 11 days.
v. large error margin: cannot really draw conclusions
(only 4 animals) - no tie could.

possible blocking in high dose in first few days at low
doses = not rapid clearance. 0, 3, 10 & 30 µg/ml.

Continued exposure

How does this data compare to doses of TPM affecting
clearance in humans (- not clearance - inhibition of cilia)

2028541463

re number of propagating AM - pooled data - initial \uparrow then \downarrow .
are the bands propagated or stuck to the surface - area of
containing in literature.
small monomers / lymphocytes? - difficult to differentiate in
flow cytometry - double labelling immunofluorescence assay.
Comparison of rats from different suppliers re health check.

Kinase - are no further data from that of Walt sent re Bremen.

2028541464

Japanese study - Hirotsugu, A. vs. dense cigarettes
Asano, M., Okubo, C. & Sasaki, A.

Establish methods - 4 wks atherogenic diet 10 rats

Blood - Chd T_c, LDL, HDL
coronary atherosclerosis & urine.

Biochemical analysis after image analysis - after fixed
mayor may not wait.

Further method depend on blood parameters & accumulate background
data on rodents not on atherosclerotic diet

* additional specimens & images.

2028541465

Monday 27th

Hub

Telephone Javier Braña:-

2nd week in November - PMCS Brussels office on
ETS & all issues... Presentation in Spanish
related to advertising.

* Last week November Tuesday 23rd 26th Vendredi. *
Talk to Helmut - can we prepare some sort of legally
cleared handout with a few "approved" annexes
to send to PM Madrid to cover up to 40 minutes on
current ETS / IAP issues?

Andy Nelson SIDS:- comments by Friday

10:00 meeting on 14th October. - will try to confirm agenda for

King Juan Warren - Friday ~~is~~ no good - stick w Thursday or
try another date..... ?

Try - ~~Andrade~~ - re Spanish presentation on ETS... idea of "general" presentation

Richard - anything re Spanish ETS. Affr
- ~~beetle~~ - ~~Warwick~~ group also

King Braña - Huber workshop studies & broader Friday ~~is~~
Spanish IARC Barcelona. -

Try - Warsaw 00 48 2 6306306 (Norriott)

Peter Heill - wait until questionnaire available.

++

Miscommunication re Huber conference - Czech in Prague - "need to
attend conference". - alright that he should not attend

Helmut anticipating that Palacios - attending the conference
Helmut faxed letter to forward to Palacios.

ETS correlated to Suicide / Homicide

European Map - LC / Air Pollution?

2028541466

Progs from Matt Winston via Bob.

S&T objectives regarding IARC:-

- * Analyse questionnaire and quality of data obtainable therefrom (e.g. ask PN how to analyse)
- * Does ~~design~~ deal with confounders, adducts (?), confounding measurement. breast cancer metastasis & general weaknesses present in previous ETS studies?
- * Assess each study group for ETS & epidemiology.
- * Prepare literature review on epi-methodology
- * Evaluate other similar IARC studies in comparison
- * Do IARC have "criteria" for conducting Epi studies
- * Through SHB & ADS identify consultants close to each of the 11 centres
- * Hazelton & Makunowski data - evaluate feasibility of presenting to IARC.
- * Evaluate feasibility of supporting confounder workshop.

Ring John Warren:- 00 46 8 729 4947 - fax?

Dund Warburton:- away for several days!

2028541467

Wednesday 29th.

Prof Claude Burker 33 1 44 27 57 04

B1002.

Basic Research study on the Biological nature of glycolysis with different water concentrations.

John Wahren 10:00 pm stay in Zurich - morning train to Newcastle or Zurich Airport.

Decent Hotel at Zurich Airport -> 10:30.
Send fax with arrangements.

Telephone conversation with Philip Garibecini in Ryebrook -
Corporate Affairs Manager for Latin America.

Explained the situation re the Farmers presentation - He will try and find out what they have on file for organising, etc etc

Thursday 30th

Re Müller work - what have Chetaniare; Sulphydric radical compounds got to do with it?

Talked to Richard Denis Giggins "Zhu" letter - will send copy to me & Libby.

② ApoE - will send over some more papers with respect to smoking for me to review

③ Filled in on Rylander conversation re confounders etc.....

Rang Odd Nilsen - not back until Monday.

Saturday morning:- Today programme - Canadian broadcasting
Toronto Western Australia

Finance Office/University of Reading
Send directly to David Warburton
Bill for 19,043. B.C.
exchange into GBP.

2028541468

October 1st 1993

Parental smoking after pregnancy and sudden infant death syndrome.

? Do studies measure 'exposure'?

? the other possible confounders fully considered.

? when were parents smoking - before or after death of child.

6/14 did not separate after smoking with smoking during pregnancy
The one which did take into the potential confounding factors into account.

Adjustment reduces risk by 46%.

Plausible that confounders could have accounted for a substantial part, if not all, of the observed associations.

An artefact of sociodemographic factors.

causation far from proved!!

∴ Bullet points would highlight - what is SIDS

what may be confounders?

role of sociodemographic factors?

Refer Lee wants to talk about mortality/morbidity, attention, talked about presenting to a wider audience - problems with collaboration - Ray Thornton suggest may be undertaken by advice to separate parents in the afternoon
But prepared to make office's available -

2028541469

October 4th.

Preparation for TAC meeting 11th October 1993:-

1 hr to discuss Technology support function; Peter Lee contract & Request for research sponsorship....

Lee/Dot - does this fall within Technical support function? -

Cigarette ignition propensity - responsibility should lie at least in large part to furniture manufacturers etc....

Phone calls

Peter Lee Diagnosis of Lung Cancer - collected additional data

- after meeting in February - suggested more work that might be done - Lung Cancer paper....

Invitation for p.m. to discuss - possibly have dinner?....

Lung PN Lee -

Keri Daines Wynder Conference "significance in Risk Assessment"
"Toxicology forum".

Keri Daines OT1 236 0066 x 5349 Keri Daines

Conrad better to be avoided by unprovenably.

Rug Andgo find out about normal procedure for TPRT meeting:

check out the past

2028541470

TPET studies of interest: #8 - Peto,
#12; Dr Peto, cloning cons - sex differences.

-4-

5th October 1993.

Conversation with Tony Andrade re Peter Lee.

Original agreement was for £23,000 with specific delusional
and then in considerably higher than the original discussions.

Funds for the review of previous publication not included.

23,000 includes 2 publications - 1 on accuracy of diagnosis
in general; one on lung cancer specifically.

PN Lees was on meeting in February.....

£700 requested for further data on FH cases - approved, given?

Future work

To look at centre for pulmonary research data in comparison
prospective-type study on smoking habits & other risk factors
in a hospital ward.
Hospital case-control possible in d.c.

Requested Total of £16,750 which was turned down
only the £750 was approved for the 67 person follow-up

2028541471

OPCS Smoking Among Secondary Schoolchildren publication
will released on Monday 18th 1993.

—H—

Hazleton study:-

4 objectives:-

1. Range, mean & median levels of 24hr exposure to nicotine & ETS particles in British Non-smokers.
2. Assess the contributions to total ETS exposure from the home, the workplace, leisure and travel.
3. To assess whether non-smokers who are married to smokers have significantly higher exposures to ETS than non-smokers married to non-smokers.
4. To compare questionnaires, direct measurements and salivary cotinine levels as methods of assessing exposure to ETS.

327 non-smokers - Special monitor for 24 hours

contribution of ETS to the total particles collected was assessed by UV, fluorescence & scintillation measurements.

Time-activity diary @ Time-activity diary - Questionnaire

③ Cotinine levels saliva etc. - post & pre-samples

N.B. ? Questionnaire did not look at other forms of nicotine use - gum, patches
all had to be rejected for smoking = misclassification!!

Summary of misclassification (not an objective of this study).

7 admitted smoking during monitoring

12 admitted smoking since recruitment but not at monitoring time.

= 19 misclassified non-smokers

34 w salivary cotinine > ~~200~~ 1000 pg/ml - is no other nicotine use i.e. smokers.
∴ at least 5% misclassification of ~~non~~ sm as n.s.

Subjective assessment of 24hr sample compared to other days -
much less than normal exposure to ETS
less than
fairly similar to
more than
much more than. ...

PAS = particles from all sources (not TSP because probably none > 30 μ m)

2028541472

TSP > PAS > RSP

ETS particles most reliably measured by standard method.

Fig 4- suggest 3M maximum higher than PM. Does this suggest that some standard detected PM are not fluorescent?

few cases below detection limit estimate $\frac{1}{2}$ det limit value....

for UPM & RSP (PAS) = 31 179 $\mu\text{g}/\text{m}^3$ - very minimum to quantify NS composition in terms (33 86 resp)

* "Cigarette equivalency" - with wedges.

PM₁₀

15 cigs/day while 150,000 μg PM during 24 hrs

Median ETS particles $\Rightarrow 2 \mu\text{g}/\text{m}^3 \Rightarrow 4 \mu\text{g}/\text{day} \therefore 8 \text{ years for 1 day matter}$

Mean ETS particles of $12 \mu\text{g}/\text{m}^3 \Rightarrow 288 \mu\text{g}/\text{day} \therefore 321 \text{ days} = 1 \text{ day matter}$

Max ETS particles of $159 \mu\text{g}/\text{m}^3 \Rightarrow 3816 \mu\text{g}/\text{day} \therefore 39 \text{ days} = 1 \text{ day matter}$

Nicotine

15 cigs/day smoker 500 μg Nic 24 hrs

Median ETS = $0.3 \mu\text{g}/\text{m}^3 \Rightarrow 18 \mu\text{g}/\text{m}^3$ via 24 hrs 73 years = 1 day matter

Mean ETS $1.4 \mu\text{g}/\text{m}^3 \Rightarrow 41 \mu\text{g}/\text{m}^3$ via 24 hrs 367 days = 1 day matter

Max ETS $26 \mu\text{g}/\text{m}^3 \Rightarrow 644 \mu\text{g}$ via 24 hrs 24 days = 1 day matter

Obj 1

ETS contributed to particulate only around 71% (mean)

Subjective: direct assessment suggest for majority of these people ETS exposure was very low.

Obj 2

Distribution below, work, home travel - Subjective -

low work > home > travel

Direct measures for single source ~~subjective~~ individuals -

Home? Below? work?

Computed suggest Home? low work > travel

p22/34 - I do not see how this calculation was made.

Obj 3

are non smokers married to non > non married to non.

subj & direct exp. nothing because > no spouse or partner > no spouse.

2028541473

but distribution shows no clear distinction - considerable overlap

P45 - mixing importance of subjective measures.

clearly criterion of smoking pause is not enough.

~~Diff~~ Days in ETS exp for these groups is significant.

Objective 4 Compare questionnaires, direct measures & salivary cot.

Salivary cotinine v. poorly correlated to subjective

Much overlap between subjective & directly measured.

~~Coordinate~~

4

Orig: John Carroll
AIN
Phil Cambocini

October 6th.

Paul Magillane, Helene Lyberopoulos.

1) coordinate days "training" with R&D.
Ask all re R&D seminar.

2) Journalists

3) Informants

4) IARC

S&T brochures.

ARISE

Smoking statistics to start. . . .

Dry run of presentation during "training" visit

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Telephone conversations with - Not in.

Canadian broadcast; Sweden

Exposure - Scandinavia - debate dinner - A little of what you fancy ^{does you good}

Charles Hayes - London Newspaper - very impressive

BBC world service satellite

Follow-up - Office Science Information Centre

Dictate letter to form a network with reading as a hub.

have 3 other people just to join the debate.

Other coping strategy reducing stress - positive effects

positive effects of immunocompetence \therefore being happy

Bereavement \rightarrow risk of cancer - Institute of Psychiatry

2028541474

rats as models

Physiological factors in cancer - medically for health.
Unwinding after stress -

—4—

lab reports:-

8/10/19:-

Artemide 215 - on cigarette paper

0.0.21, 0.49, 0.82 & 1.29 mg/kg 6/11/day, 7/11. 90 days

TPM conc = 101 µg/l

⇒ slight enhancement, of goblet cell hyperplasia

" " atrophy of nasal ducting epithelium (trachea)
respiratory cell hyperplasia. (and serous)

⇒ slight enhancing effect on biological activity.

2 series of wgs:

X6DOCEM, 0	X6DOCEQ	0
X6DOCEQ 0.21	X6DOCEQ	0.52

X6DOCEP. 0.49	X6DOCES	1.29
<u>15g</u> mg/kg	<u>25g</u>	mg/kg.

= diff only in paper weights

Diffs between series 1 & 2 in formaldehyde acetaldehyde acrolein

NaOH	0.26-0.29	6.9-7.5	0.28-0.35
QES	0.11-0.46	8.2-8.7	0.51-0.84

QES also moved 20% lower & 80% higher nicotine.
group QES have 1% citrate in paper also.

5/10/20:- cigarette

Hyperosin changes in classical, & 4 in adrenal weights.

not related to humidity. but more pronounced in 'matted' dry.

2028541475

B1018 -

Propylparaben as filler ingredient

250 & 750 ppm. 90 days

No influence. ...

250 ppm showed less active for nerve cell hyperplasia, sq. net

in nasal resp epithelium.

sq net - normal af. epi.

goblet cell hyper.

epm almost.

But no explain for why? --

Staff Meeting October 1993.

Warren 24,000 \$

also for next year.

1 PM → Druggins next week
Smith's review.

Setton Meggins

Salomaggiore book published ...

Pershagen - reports next year preliminary evaluating serious ongoing focus on cardiovascular disease possible next

① re CVD - JW cannot see potential mechanisms - could dip organisms along their lines - analysis of levels of substances in ETs etc....

~~Prostate~~ prostate cancer inhibitors produce "document", paper on all factors.

e.g. Pamin making similarity to effect with testosterone substituting to alter apoptosis levels.

② Nicotinic & CNS function: Total blood flow NME, PET:

PET blood flow, NME circulation function in brain.

Global blood flow under nicotine exposure - no net change

but could be redistribution regional aspects of uptake

can image changes in reduced hemoglobin w NME receptors

w NME - could detect changes in signals w time

have artifacts appears NME not working in turn respect!

PET activity task - have more while test takes place!

∴ NME appropriate to study brain performance when brain is active

2028541476

every 15 min inject 1' O⁵ labelled butanol ~~concentration~~

⇒ Byt bars w t least nicotine infusion.

⇒ 4 in cerebellar bloodflow but 4 in visual cortex.
but cannot be sure if related to nicotine itself!

To continue with 4-5 patients → US, 000 sec. (2 CHF P, 000).
More data needed....

+

Verbanat - (Venun). - Adlger. Not submitted because of NME
outset. - ie then PET will be a pilot study for neuroimaging
as a larger study later on

PET and alzheimers & nicotine receptors.

One defective target could be in brain disease mechanism Parkinson's
and alzheimers.

+

③ Information Board disease - Ans to send references to John Wahren
Therapy(?)

—+

④ Nicotine meaning - Conrad & Wahren. Nicotine metabolism group
Raymond group

Details of Nicotinic conference to John Wahren. Glucuronides / Retenes.
Presenting April/May 1994. Nicotine metabolism? Pharmacological studies.

John & Me to discuss topic current - must progress have new data/there
Ruth - John on return from trip - early version.....

⑤ Energy expenditure Nutrient induced thermogenesis - protein - high (yes)
10-12% energy expenditure during smoking. ^{fat - not used}
_{chole - internal energy}

Featuring

Brain adipose tissue generally lost in obesity - except in
exceptional circumstances - maybe involved in thermoregulation.
Brain exert influence on inhibitory output even though may
& nicotine exert an effect in this regard.

Maybe adipose effect on energy expenditure & blood temp after
a meal

⇒ more appropriate to Venun? ⇒ John to submit proposal.

2028541477

Tony Andrade: Medical expert in Finland.
Industrial Inguenit.

ITPAC: October 14th 1993.

Responsibility to scientific group to maintain function only as necessary

LCC - attempting to publish data over October 1992 & maintain
volition with valuable data of above 15mg because it caused the
translational period where 15mg treatment was bought in.

ITPAC, Doh, LCC & company representatives minimized meetings to
drawn all their points.

Terms of reference of scientific liaison group with LCC - must be done
through emerging liaison group.

Respectful liaison & Asthma documents not cleared.

Clive Turner - ASH newsletter withdrawn from Australia - heavy
on Asthma & primary health issues -

Clive to be given exit letter on advice involving
Theraviva

-4-

Peter Lee.

Asthma retention account for time £20,000.

£16,000 - "overhead" expense.

THE cannot be interested in non-union organizing other than ETS.
Any X's historically been charged to the
Doh & contract specific to ETS - comments within 1 week.
overall down from £16,000 with marketing accounts.

Request for research sponsorship - general product
advice within legal but not happy with it.
Bair formal warning

SABs weighed averages proposed to Doh - but probably not want
continue to collect data and eventually will submit to Doh,

2028541478

TPRT.

currently ongoing.

8th term report would be rec'd in next 2 weeks
project 25 & 26 research being used for other things.

para 13 - submission - critical comment - 2nd paper to be submitted.

Theme of annotations -

+ve balance at end to go to chairing as agreed previously.

Interpretation of findings by trust

Waller - original degressive was under compensation.

Reinolds - kept up with science - genetic haplogroups - mol biology etc.

∴ Trust with the field all the way

Sutton - compensation? - Waller early studies showed some compensation but more recently - with very narrow range of production don't really see any degree of compensation.

Reporting of all the projects to be discussed with TAC

TPRT - Waller - will leave a great hole in research
Doh will keep an eye on this and we can expect both to come
up with some research but not as good as before more
or an odd hoc basis.

Forget Neth Res Council. - cancer & smoking 60% funded through

TPRT.

TPRT users - unique - probably won't happen again

Future - TAC keep in touch? - yes.

Next meeting probably next summer with ideas for final report

2028541479

11th Oct. PM 100.

Colnate study - looking at trends in mortality with smoking rates but not always smoking rates available. Started with U.K. - modelling etc plus estimates of historical consumption data.

lead to 1000 paper Tobacco 1000: 1951-65 - ①
women le not + since war in cigarette smoking.

* Barker book - infant mortality in HD & chronic Bronchitis, now a very high correlation - Trends in smoking related diseases may be due to trends in infant mortality (mortality?)

3. submitted and never published because smoking data was only sales data and not age and ex related.

Oswald and Gardner approach to model mortality rates with the future (up to 2003) seen to show changes in "smoking" - fairly well confirmed on a method.

used better cigarette consumption data... → international smoking mortality book.

International tobacco weight data may be the Method to give standardized data in 5 year cohorts to fit with mortality data - available on request.

Roselle database

Mortality rates, 100

eg Sax: ratio M:F 1.45 - remains relatively constant in spite of effect of smoking getting closer together

Could be available to work out own needs or find further work - newspapers of database

First step should be to look in more detail at country conventions w smoking related diseases

2028541480

Francis Roe / Peter Lee :-
FJCE

EHC/GPS series 154 (latest) "erudite little book" on cancer and significance of ageing.

Hungarian study:- lung cancer paper to be produced no more charges (unless possibly minor).

Could proceed either with case-control / major study for which much money and great planning would be required including a 'criticism' as unknown!

or continue to data dredge:- relatively cheap but may not give good quality results - the free felt that there was still more information to be gained regarding e.g. reasons for mesothelioma; such as not enough time between admission & death; too ill; maybe association is socioeconomic status etc etc.....

-14-

Re passive smoking epidemiology - mesothelioma of NS which were in fact ex-smokers. The ~~the~~ Abdi preliminary paper only really assesses reliability of questionnaire compared to recent smoking status - well known that ex-smokers nonrepresentation NS more often than current smokers.

2028541481

25/10/93.

d. Limonene - ♂ rat kidney tumours. α2-microglobulin - only metabolite
no human analogue of α2-microglobulin. - not neurotoxic, eliminated
no known animal carcinogens on ingredient list.

Trans-anethole.

gum 2-600 ppm up to 2500 ppm

structurally similar to safrole, DHA & estragol.

Ames assays - negative except one study w/out activation '79 & '82
& one acv S15 mutation in v acv TA100.

DNA repair - positive

when epoxide - active.

Carc studies '83 mouse -ve, but exposure only 12 months, one sex

46% - weight loss but not specified how much

'89, ~~Thunberg~~ ^{Thunberg} study rats +ve benign & malignant

but not unique to exposure group only at high dose, only 8%

Not sign diff from historical range

Newburn study '89

Metabolism studies shift to epoxide at high levels.

JEOP evaluation in 1989. - call for more studies on metabolism
and role of epoxide in the ♂ rat carcinogenicity.

October 1993 status of FEMA studies.

Mouse lymphoma - +ve but only one

so far no clear evidence supporting the epoxide pathway

Metabolism studies - rats & ♂ epoxidation P450.

Mouse model 7 cyp P450

1% group had some minor changes.

Not low enough for no effect level.

Reevaluation of rat 2 year study. 0.25% NOEL for peripheral
epidemiology - no effects.

FEMA draft by end 1993.

Estimated intake in cigs worst case - 4.5 mg/day

current ASI - 23 mg/day

2028541482

* Complete Gerson's feedback list. 3 Dams vs. 11 dams

Thyau ya p?

-1-

Monday November 1st

1) Expenses.

- 2) wife - visit with Nitch...
- 3) Ring Conrad - Books, Bill, estimate(?)
- 4) Ring Phil Gambaccini - SA 253

Phil Gambaccini - bug! Phil Gambaccini. // Pigs dead
Jewier Brother S.A. 216 with.....

N-hydroxy methyl voronine -#
[16h] M. Jacquet - November 16h.

* Fax to John Conrad. *

Tuesday Nov 2nd

Patrice Club de Patineurs Nov. 2nd. 33 W 1 85

Mardi et Jeudi 3/4 hr. 16h 16:15 230. - funtion
abonnement

privé → [Belcote Grosard 25 72 50]

-#

* Arrange to see HCA re REDSC

* Talk to Ted Sanders re Tok stuff

* Arrange to see J-J-P re ETS issues.

Wife - Nitch given ^{evening}

- Pany restriction lengthen polymorphism. Restriction file mutation

-#

Aurora Gonzalez - Vaccines until Nov 2nd.
Matt will ring back!!

2028541483

Odd Nilsen:-

Problems in extracting nicotine on 1.0 μ Fluoropore filters for
radio partic / vapour. Nic vapour by RAD tubes = already done.

- 1) - Is this from the briefcase sampler?....
Any samples left? ----
Want comments on method or what?.....

Fax: letter of Odd Nilsen to WBS
David Warburton request re ARISE to
Ring Peter Lee - re RISC project.....

Ring Reinhold Nilsen papers - treated with confidentiality.

- ② Nilsen has request for information
- ③ David Warburton letter
- ④ Mith re TARC - presentation - visit P....
- ⑤ Hum December no good!!

Write to David Warburton - Thanks!

Beginning Dec - start No
Collyer files

Dec 10th / 10th December
→ Tony Andrade - Hungarian, Italian, Chinese papers.
Include Peter Lee Hungarian study.

- 1) Ring Peter Martini - send ARISE stuff etc etc.....
- 2) Ring M. Jorgensen re meeting - key in book on labor 3-9-84
- 3) Tony Andrade - Peter Lee, Francis Roe Hungarian Autopsy data etc.
Hungarian / Italianai.....
- 4) ~~Ring~~ to David Warburton with thanks - Ring regarding new arm with
Nilsen.....
- 5) Ring Peter Lee re mortality prediction from epidemiology.

2028541484

Get Nilsen with Minkung.

Peter Lee:

specific reviews on predator papers Swartz & Mendel.
wildlife publications in this area? - what in the general
Richard Bell - got it write

Emily Andrade:

Peter Martin.

Details of Frank McKenna's many publications -

TDC - data

Books - Digby Anderson Social problems.

Thursday 14th

Kneeling 11:00 - 11:45 *

Ring David Wardlaw.

Frank McKenna University of Tennessee 784-3189330

After Peter TDC address & no. 14

Digby Anderson base - social problems Peter Strabawek 1st paper?
Papers from Frank McKenna.

Maximise Agenda for Boston Ideal Agenda on ETI values

2028541485

Spanish ETS presentations Agenda

introduction to S&T.

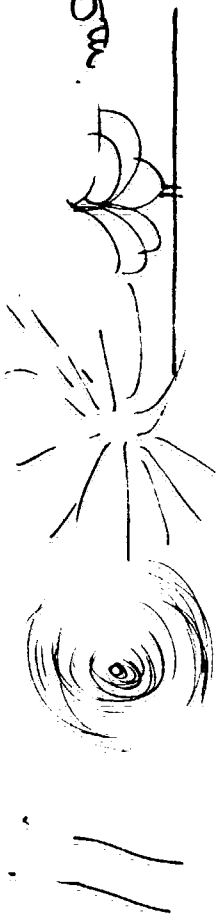
- 1) Discussion of experiences with African - Grouper etc.
- 2) Presentation of videos
- 3) S&T ETS 'National' - workshop involving laptop etc etc } RIT.
- 4) Workshop on Corporate Affairs etc.
- 5) S&T project profile & review of strategy for 1994
- 6) Values of importance in Spain - Grouper / Journalists
- 7) Plan of S&T contribution to PM Spain CA.
- extent to which S&T ~~can~~ have resources to provide material in Spanish.

Re presentation:

starting 'ETS'

Punto de Partida:

Friday November 5th.



1) Organise props to everyone checking on invitation to Javier Braña regarding agenda etc etc.

2) Organise Agenda for Javier Braña !! - check with Nitzel, IAM etc etc.

3) Check Prop !!.

2028541486

Friday November 5th, 1993.

Nylar: 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine.



$C_{20}H_{19}NO_3$ Mwt 321.37.

~~Final~~

~~Final~~

+

Ring Peter Lee - risk projections, validity of population based

- multi-stage time trends etc etc.....
- Japanese study.

write David Warburton - to confirm 24th

Develop Agenda for Brazil - 1st Dec ?....

Develop Agenda, ideas for Tokyo.

~~check~~ ~~ear~~ ~~situation~~ ~~with~~ ~~fall~~.

Write to Nilsen, ring Nilsen.

TAC- check-up.....

Ring Webb - re Nilsen request.

2028541487

Monday 15th

TAC

1. "How the other side" - out but no copy - someone get...

Report received revised / finished version by Xmas 1993.

2. ETS summary statements: tests - exposure markers; considered
current summary - no change workplace - should perhaps try and
cover this point re workplace studies

Dan Parkes correspondence re forthcom - not significant - although
in our database we have it down as significant!

Lui - nonsignificant - but subgroup which is significant

Pompe approach - rather accept surface value studies covered
not estimated (unless study reports it) - if a study does not
report an overall risk then PNI should be asked to calculate
overall risk - This would put forthcom as nonsignificant.

John Lewis: Barbara Box - stated Githam significant

Comment from referees - did they use both one-tailed test and PNI

* Jane McStroud Box considers letter to Matt Windsor

re Lui - should stick with overall risk & not subgroup

* Further 3 yrs of Sys paper - probably completed. ETS, LHC, Canada Bull (SC)
conclude - 30% risk copy to be talked & PNI

ETS & C&L - see sheet. LHC resubmitted to Karl Dan.

ETS & ASTMA - Nottingham University Study - Early Day Motion by M.P.

Aspiration & Asthma - John Ayres M. SC etc etc - Ozone
from Pulse.

- re Grouping for Breathing from CMC Thinner

NS Asthma we may have to go back to comparing lawyers re common

More emphasis should be given overall in overall ETS summary

Maximum studies

Group should train for comparing useful information to share with the
Group

2028541488

John R. Conditate with Karen Ashmore

are ~~planned~~ ~~not~~ in the factor taking into account of the
 effects for ~~measuring~~ measuring them (within ref)
 The latter

circulation of the market, support price being adjusted with the
R.P. to the R.C.

~~Handwritten~~ Handwritten Reference - Kontakt zu für comments / Expert views
- 10/11

*Chile Tumor - Hit by woodcock on Radio is important labelling

Netherlands - PN Lee Correspondence

PN has suggests indicating Branson & Stockwell will look at significant
 study, I am to pick up with him. ~~Refer him back~~
 the name Christine researchers.

B test

cannot do maternal pregnancy smoking & per pregnancy. may not be able to cover because involves 'active' smoking

Other media - leave in - develop

Decorating fishes - focus on bottom right +

Parental Smoking & Childhood Cancer - NCI had mortality position.

ETS & Radar - APN no time to do. ask Police to review it again
(update old version)

Ext Analysis 12(6) CO2: Quantitative Response ETS & Policy - ARI to
direct to Policy

References to additional references:

Rate too will no longer work and under paper epidemiology on

✓ active issues (primarily women) - need to do directly w/ PWR
✓ see proposed on Twitter like

control group - only group which receives electricity with PHE

To be discussed next week.

2028541489

Any other business:-

the newsletter

* National ETS meeting Washington September - 1993 sponsored

ETS. Current Assessment & future direction

the Attach will summarise various papers particularly Reichenberg & Ti

* Lecture 1st interview Transcript - Dave Rowlands
⇒ Matt Winkler.

Recent journal publications of ETS Science & Politics

u

Glantz & Paruley PM Formic acid & HD; Genol, Physiol
Blood Chem.

Prep for written Friday

Odd Nilsen:-

clarification of hair structure - surface area
humidity uptake as characteristic

Hypothermia re uptake. 2 phases - absorption & adsorption.
Adsorption must penetrate cells!

Radio labelled nicotine + EM or Radiochromatography

Scanning EM & transmission EM.

structure

localisation - IR microscopy.

Nilsen to contact Norwegian hairdressers re structure of hair etc
Manufacturer eg L'Oréal etc

* Compare ^{probe} levels with detection limits of breathalysers.

Breathalysers measurements correlation of TPM, INR with CO₂ (probably)
but tremendous variation.

Point to be made in paper - need for bio measure -

diff bet cotinine & nicotine v hair - much better long period

2028541490

Kiri Jones - sending all exposure Maudie stuff

23rd November 1993

George Patskan: Materials evaluation: database
journals / reviews...
criteria?
list of non-permitted.

Ring Peter Lee: Swift 2 paper.

Ring Helmut Causch:-

Peter Lee: In order to be sure need considerable more work

2 problems - model - multi-stage model = initially identical to one developed by PN Lee & others in the past but to what extent does ~~that~~ the figures depend on the model.

comparing smoking habits of people born 1965 ish to 1920.
(Hammers smoking data - suggest that 1920s group may have smoked more in early life & less in later life compared to 1965 in the contrast smoking group)
Model accounts for this to some extent.

other problem - how reliable is the smoking data -

All came from one large survey at one time point
- no validation against sales - survival only.....

2 or 3 months to get into it - to using our data.

to write some brief internal review

Quite odd relates to something relating to the database etc
anyway - \therefore possibly could do with

HCA:- la Postole 68 - 2036 Comandache: 30 32 34.
(fax) 30 32 35

Waf:.

Skrobaneck.

2028541492

George Potstain - How much are folks really being exposed expecting to get more detailed analysis of this paper -

Tex to Cathy - database - currently an E&D computer system
How handled here - diff factory locations each have a representation which access through a modem

Get rid of P&G list - more recent list by folks in Q.E.
(= functional group responsible for industrial materials evaluation
- Program only considers functional use in these or other alternatives.

List just published generally not recommended materials
also document describing the workings of the system.

Provides a little bit of information re chemistry & toxicity
- often eg. Dow deodor - just MSDS.

Buyers in direct contact - what if it falls in 'pyrolysis'
Engineers - input regarding likelihood of contamination.
Probably industrial hygiene - not as great a consensus ingested!
H

Green Tobacco sickness - ABC news article - re tobacco farmers.
- had any
--

Fire safe cigarettes

Jerry Wullday . . . ext 5276

Some cigs - survey vast majority of fabrics not ignitable
Materials
∴ not going.

∴ not realistic to develop a cigarette

v. extreme cigarettes - even more could parallel
tobacco!

Get back to Jerry Wullday action -

Major argument that design of cigarette not possible to rig
Manufacture potential!

2028541493

26/11/93

*Tang Andrew -

Bill James Report - Nitrosamine have been down as
skin & other injected - check - feeding studies

Nitrosamine skin painting -

Alan Bras

send Addition list - ADA + ingredients

- May/June 1993 -

BAT → indicating to insurance firms Andrew Fife
legal issues - to insurance personnel - not to settle
to ET in the workplace -

More likely to use the case & more likely than
anything.

not too successful - but no feedback

going to outline law firms which represent these
insuring companies - advise insurance

Gray Huber - FICR Handly -

John Melton -

BAT; (Fife M) Robinson Galleries & Imperial (+TRC)
in House Council -

*Tang Peter Lee → IARC * Accountancy

* Christo Jones *

* Judy ... *

→ way ... *

2028541494

MS / SS NNK measurement - 4 conc - artefactual
formation in particular -

Nitrosamines as Biotrans.

ng SS - preferentially artefact much more than

sample for (the) MS - could be higher or higher can
impregnation of filter

MS → B₁

SS →

30 ug, in a room 4 flattening out deposition -

15 ug - dark red half of this

et - - exponential →

more dense the saline -

Martin R. Rieckner (y) -
intermediate TASSO

Tony Andrade - "Caution" - never "Ingredients".

[But Tony's Nicotine numbers much]

Certain ingredients re. food - use to examine
objective → to inform the consumer.

Note to Chai = another same diff. in that food
does not provide all information
categories.

if drugs come up - protected by patent.

can disclose trade secrets, complete
information.

2028541495

PNHlee

Order 10:00

IARC: Meeting Paris/Venice before the end of the year -
schedule a meeting to Riboli/Suzuki regarding
this project expressing ~~concern~~ / sharing latest data
findings Japanese study etc -
Methodological concerns re exposure & misclassification
- sensitive to eventual weaknesses to improve precision
reliability etc -
If possible get invited to their meeting
get an updated questionnaire
an update on status
try and get an idea of any divergences regarding info
what confounders they are considering

We will pay for

// Amendment to public report re public transport
Wed. p.m.

PNH. BMJ rejected Japanese paper - big review by "Wells"

notable difference main re industry vs nonindustry

- don't cite all - don't refer to EPA report

Sample size too small - confounders

age range not representative

General Wells - "made-up" =

Authors note funded by several tobacco companies

should specify tobacco companies

* Lancet - necropsy study rejected }
Human Exp Toxicology accepted }

Morris review - Francis & Lucas take both sides -

combing but would not act as a supplement to BAT.

Sample autopsies are previous years re contribution
over last 100 years

2028541496

Monday, 29th Nov '93

Workplace meeting

King said other tobacco companies re PNLee.

- ① Profs to Borden.
- ② ~~TAC notes - extract text.~~
- ③ Telephone notes re PNLee
- ④ Profs to Wolf re meeting agenda.
- ⑤ Profs to Greg Fowler.
- ⑥ Brouce arrangements 'response to Hecht paper and other miscellaneous stuff'.
- ⑦ ARISE: * NORBERT, GENSARD - BOE..... French. *
- ⑧ TAC filing = # JUL.
- ⑨ send Richard Harris stuff to Wolf.
- ⑩ TAC response to Repace & Lowrey and Hecht for TAC.

Andy Nelmer:

Peter Lee

\$7,500 ->

turning to January/February, end of February/January
Appointments all before Dec 17th (Friday!)

Wolf turning hours.

2028541497

Hecht paper -

- 1) Levels of ETS exposure INNK.
- 2) Comparison of before & after.
- 3) Glutathione S-transferase?
- 4) Different levels
- 5) Specificity

Tobacco-specific

Data not new - have been found
update has been published

have to relate to dietary uptake of nitroaromatic hydrocarbons

IARC - Rogan - As far as WdJ know - WdJ on salary
Industry should propose research for next years any topic
laurel - ?

2028541498

Tuesday 30th.

Met Harker & Joana Sullivan.

Belgian workshop (au):-

consider meeting re diagnosis & health, but no consideration re exposure to other exposures eg. restaurant; diesel fumes etc....

Inconsistent with previous proposals - 12 others with no mention of smoking bars.

e.g. of scientific literature on health risks and diagnosis from other work place exposures. -

use of machine to help concentration etc - pilot study - Warkentin etc.

CHT - favourable information from tobacco side.

Best man highlighted? - Kassar.

Eng Odd Niven ... re nuclear article.

check meeting & lung cancer figures.

$$\left(\frac{250}{100,000} \right) =$$

2028541499

ARTERIOECLETHOSIS STUFF.

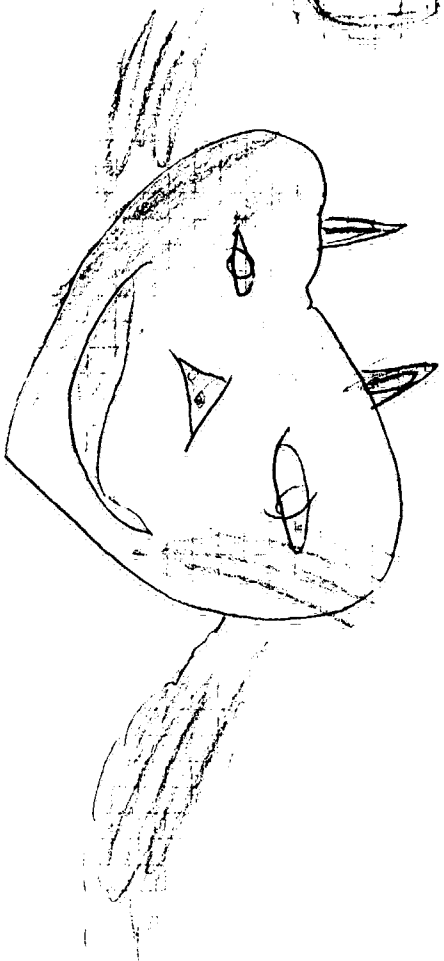
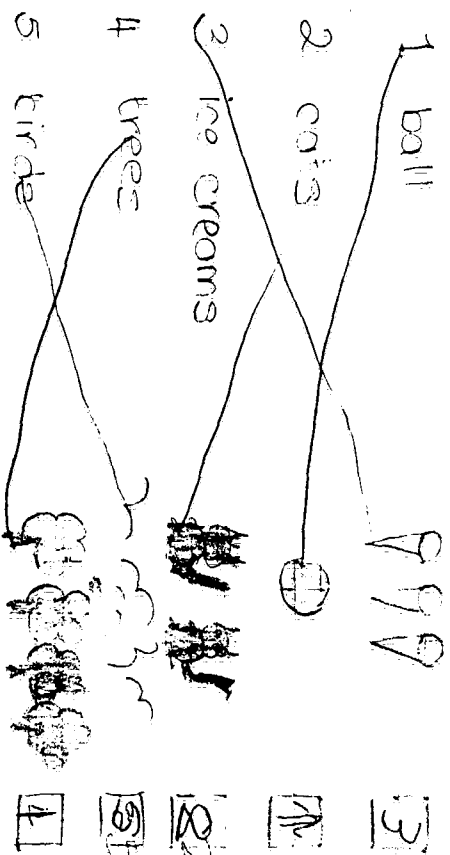
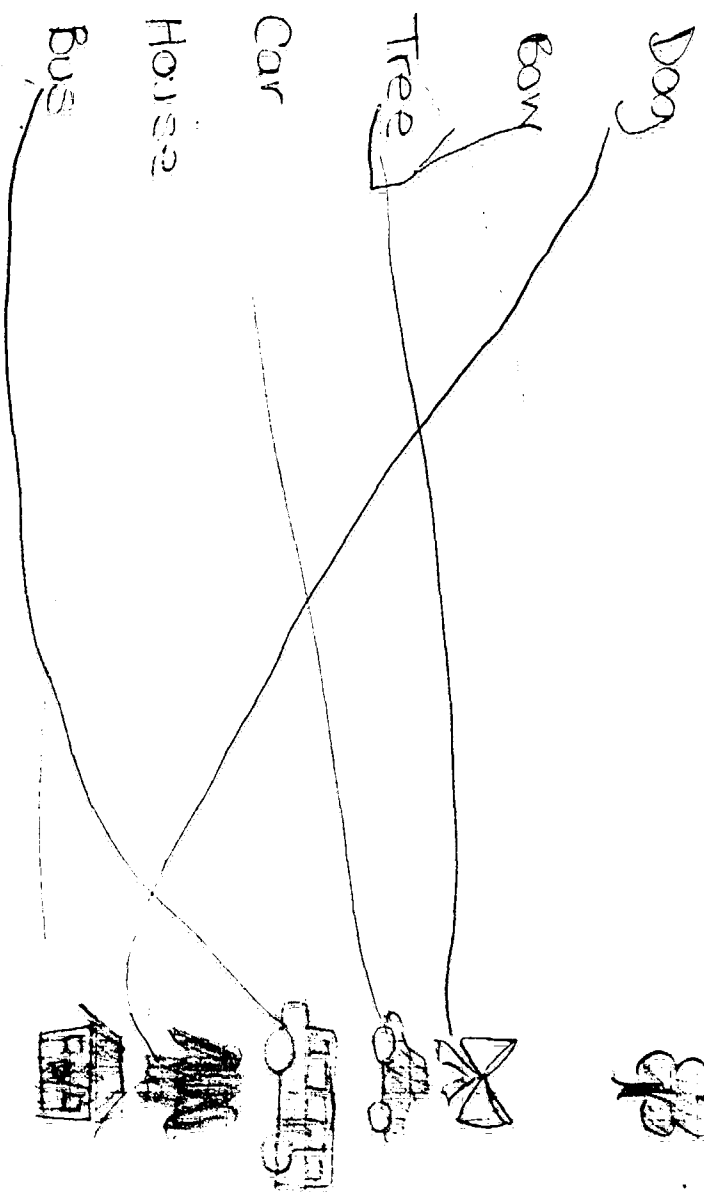
1) ~~Look up~~ ~~app~~ ~~mtg~~ on stairs....

Packing:

PN. has paper - most recent copy of
February announcement.

2028541500

Name: Jessie



2028541501

Textbook of Epilepsy

6th Edn: John Laidlaw (Eds)
Alan Richens
David Chadwick

Edinburgh - Churchill Livingstone Pp 754
£100. ISBN 0-443044732.

Wiley
Epilepsy
1992
Dox
Cunning
S 100201
St 10117

2028541502

2028541503